**Table D1. Characteristics of studies evaluating diabetes medications in terms of intermediate outcomes**

| **Author, year**  **Country**  **Registered protocol** | **Enrollment period**  **Follow-up duration** | **Run-in period** | **Planned interval of follow-up** | **Pharmaceutical support** | **Number screened/ enrolled**  **Source population** | **Exclusion criteria** |
| --- | --- | --- | --- | --- | --- | --- |
| Aaboe, 2010[1](#_ENREF_1)    Denmark    NCT00838903 | 2007  2008    12 Wks | No | Not Extracted | Yes | NR/ 24    Outpatient clinic not specified and in response to local advertisement | HbA1c >10% or <7%, on metformin monotherapy for less than 3 months, taking additional medication that affect glucose control, history of GI surgery, positive measurements of islet cell auto-antibodies (ICA) and/ or glutamate decarboxylase-65 (GAD-65) auto-antibodies, elevated liver enzymes (ALAT or ASAT) twice the respective upper normal value, elevated serum creatinine concentration (>130μmol/L), severe CVD (NYHA group III or IV), Albuminuria |
| Ahren, 2014[2](#_ENREF_2)  Country NR  NCT01126580 | 2009  2013    104  Wks | Yes | Not Extracted | Yes | NR/  1049    NR | Age <18 yrs, HbA1c > 10.00% or <7.00%, BMI <20 or >45 kg/m2, any liver disease, any kidney disease, adequate glycemic control while taking background metformin (>=1500mg or maximum tolerated dose) >=3 months before screening, abnormal thyroid-stimulating hormone concentration and not clinically euthyroid, ongoing symptomatic biliary disease, history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (<=2 months before screening), treated gastroparesis, history of GI surgery thought to significantly affect upper GI function, history of most cancers not in remission for at least 3 yrs, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, resting SBP >160mmHg and/or DBP>100mmHg, |
| Alba, 2013[3](#_ENREF_3)    Multi-continent  NCT00734474 | Neither year reported  12  Wks | Yes | Not Extracted | Yes | NR/211    NR | Age <30 or >65 yrs, HbA1c >10% or < 7% if drug naive, HbA1c >9% or <6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, duration of type 2 DM >5 yrs, any liver disease, any kidney disease, history of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week 12 |
| Apovian, 2010[4](#_ENREF_4)  US  No | 2006 -2008    24 Wks | No | Not Extracted | No | NR/ 194    NR | Age <18 and >75 yrs, HbA1c >10% or < 6.6%, BMI <25 and >39.9kg/m2 lacking history of stable body weight(varying by >5% in last 6 months), not treated for at least 6 wks with a stable dose of metformin or a sulfonylurea, use of exogenous insulin, alpha-glucosidase inhibitors, a thiazolidinedione, use of weight loss agents within 6 months before study entry, evidence of poorly controlled hypertension within the previous 3 months, history or presence of cardiac disease within 3 yrs of screening |
| Arechavaleta, 2011[5](#_ENREF_5)    Multi-national  NCT01023581 | Neither year reported  30 Wks | Yes | Not Extracted | Yes | NR/  1035    NR | Age <18 yrs, HbA1c >9% or <6.50%, not on a stable dose of metformin (>1500 mg/day) as well as diet and exercise for past 12 wks, history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable medications for hypertension, thyroid disease, Hormone replacement therapy, oral contraceptive pills |
| Arjona Ferreira, 2013[6](#_ENREF_6)    Multinational  NCT00915772 | Neither year reported  58 Wks | Yes | Not Extracted | Yes | NR/  426    NR | Age <30yrs, HbA1c > 9.00% or <7.00%, prior or current use of insulin, any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duration of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, at visit 2 FPG>260mg/dl and unlikely to improve with diet/exercise, at visit 3, FPG>250mg/dl consistently (i.e., measurement repeated and confirmed within 7 days), at visit 4 FPG>240mg/dl consistently, at visit5, finger-stick glucose > 240 or <120mg/dl |
| Aschner, 2010[7](#_ENREF_7)  Multi-continent  Not extracted | Neither year reported  24 wks | Run-in period but number excluded was NR | NR | Yes | 2068/1050  NR | Age <18 or >78 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, creatine kinase (CK) > 2x upper limit normal |
| Aschner, 2012[8](#_ENREF_8)    Multi-continent    NCT01106677 | 2008 -2011    24 Wks | No | Not Extracted | Yes | NR/  515    NR | Age <35 or >70 yrs, HbA1c >=11% or <7, BMI <25 or >45 kg/m2, duration of type 2 DM <6 months, any liver disease, any kidney disease, FPG >14.4 mmol/L, treated with oral anti-diabetic drugs other than metformin in past 3 months, received SU+MET In past year, prior use of GLP-1 or DPP-4, any disorder that the investigator felt woudld compromise the patient's safety, unwilling to self-monitor blood glucose (BG) or keep diary |
| Bailey, 2005[9](#_ENREF_9)  UK, 14 European countries  Not extracted | Not extracted  24 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <18 or >70 yrs, history of CVD, no Type 2 DM, other |
| Bailey, 2013[10](#_ENREF_10)    Multi-continent    NCT00968812 | 2007- 2008    102 Wks | Yes | Not Extracted | Yes | NR/  546    NR | Age <18 or >77 yrs, HbA1c > 10% or < 7%, BMI >45 kg/m2, any liver disease, any kidney disease, history of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, SBP >=180 mmHg, DBP >=110 mmHg, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, NYHA class III or IV congestive heart failure |
| Bakris, 2003[11](#_ENREF_11)  US and UK  Not extracted | Not extracted  52 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | NR |
| Bakris, 2006[12](#_ENREF_12)  US, Multi-continent, South America, Europe  Not extracted | Neither year reported  32 Wks | Yes | < 6 months | Yes | 560/514   NR | Age <40 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI <22 kg/m2, use of any TZD in the 3 months prior to screening, use of insulin for ≥ 6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg |
| Barnett, 2012[13](#_ENREF_13)    Multi-continent    NCT00707993 | 2008- 2010    52 Wks | Yes | Not Extracted | Yes | 227    NR | Age <18 or >80 yrs, HbA1c >10.0% (9.0% for Canada) or <7.0% for treatment naïve patients, HbA1c > 9.0% or <6.5% for patients receiving an oral anti-diabetes drug, BMI >40kg/m2, Prior or current use of insulin, any liver disease, any kidney disease, contraindication or history of intolerance to metformin, pregnant, nursing, not using adequate contraception, MI, stoke, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an anti-obesity drug within the previous 3 months, or any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs |
| Bergenstal, 2010[14](#_ENREF_14)    Multi-continent    NCT00528879 | 2008- 2008    26 Wks | No | Not Extracted | Yes | NR/  514    Outpatient: primary care | Age <18yrs, HbA1c > 11% or < 7.10%, BMI <25 or >45kg/m2, prior or current use of insulin, prior or current use of study drug, pregnant, nursing, not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 DM, FPG >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use |
| Bergenstal, 2012[15](#_ENREF_15)    Multi-continent    NCT00740051 | 2008 - 2011    156  Wks | No | Not Extracted | Yes | NR/  666    clinical sites unspecified | Age <18 or >75yrs, HbA1c > 10% or <7%, BMI <25kg/m2 (<23 kg/m2 for Asians) or >45kg/m2, prior or current use of insulin, history of CVD, neuropathy, retinopathy, NOT receiving metformin (stable dose >/=1,500 mg/day or maximally tolerated dose for >/=12 wks before screening), diabetic nephropathy, GI disease, previous bariatric surgery, pancreatitis, previous exposure to other oral anti-hyperglycemic or weight-lowering drugs within 12 wks, >1 week of insulin within 6 months, or another GLP-1 mimetic or analog at any time. |
| Blonde, 2002[16](#_ENREF_16)  US  Not extracted | Not extracted  16 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <30 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <7.4%, no Type 2 DM, other |
| Bolinder, 2012[17](#_ENREF_17)    Europe  NCT00622284 | 2009  2011    102  Wks | Yes | Not Extracted | Yes | NR/  182    NR | Age <55 or >75 yrs (women), <30 or >75 yrs (men), HbA1c > 8.50% or <6.50%, BMI <25kg/m2 and body weight >120 kg, prior or current use of insulin, any liver disease, any kidney disease, pregnant, nursing, FPG >240 mg/dl (>13.2 mmol/l), diabetes treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment  perimenopausal women, body weight change >5% within 3 months  serum total bilirubin >34 μmol/L; hemoglobin <105 g/L (10.5 g/dL) for men and <95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than 2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, SBP >/=180 mmHg and/or DBP >/=110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure; significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications); alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrollment |
| Borges, 2011[18](#_ENREF_18)    Multi-continent  NCT01318109 | 2006  2008    80  Wks | No | Not Extracted | Yes | NR/  688    NR | Age <18 or >75 yrs, HbA1c > 10.5% or <7.5%. BMI <= 25 kg/m2, prior use of any diabetes treatment, fasting glucose <7 mmol/l |
| Campbell, 1994[19](#_ENREF_19)  UK  Not extracted | Not extracted  52 wks (planned duration) | Not extracted | Not extracted | NR | Not extracted | Age <40 or >69 yrs, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other |
| Cefalu, 2013[20](#_ENREF_20)    Multi-continent    NCT00643851 | 2009  2011    52  Wks | Yes | Not Extracted | Yes | NR/  1452    NR | Age <18, >80 yrs, HbA1c < 7% or >9.5%, Any kidney disease,  Not on stable metformin therapy (for at least 10 wks  prior TZD use in 16 wks before screening, history of more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15.0 mmol/L or more during the pretreatment phase; |
| Charbonnel, 2006[21](#_ENREF_21)  Multi-continent  Not extracted | Neither year reported  24 Wks | Run-in period but number excluded was NR | NR | Yes | 1464/701  NR | Age <18 or >78 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >10%, Type 1 DM, insulin use within 8 wks of screening, FPG >14.4mmol/l |
| Charpentier, 2001[22](#_ENREF_22)  France  Not extracted | Not extracted  20 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age ≤34 or ≥71 yrs, any kidney disease, history of CVD, no Type 2 DM, other |
| Chawla, 2013[23](#_ENREF_23)    India  NCT00798161 | 2008  2009    16  Wks | No | Not Extracted | No | NR/  52    NR | Age <18 yrs, HbA1c < 7.5% or >11%, Any liver disease ,Any kidney disease, History of CVD, not on metformin monotherapy of >=1500mg/day for at least 1 month, FPG<140mg/dl or >270 mg/dl |
| Chien, 2007[24](#_ENREF_24)  Taiwan  Not extracted | Neither year reported  16 Wks | No run-in period | < 6 months | Yes | 166/100  5 medical centers. Does not specify inpatient or outpatient | Age <30 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, retinopathy, HbA1c > 12% and FPG>250 mg/dL at screening visit, HbA1c < 7% and FPG<140 mg/dL at screening visit, BMI <18.5 kg/m2 or >35 kg/m2, current significant GI disorder, hyperglycemic hyperosmolar non-ketotic coma, hypersensitivity to glyburide or metformin, current infection, treatment with insulin in last 6 months, surgery in past 4 wks, history of cancer in 5 yrs, on concurrent drugs affect sugar metabolism, FPG < 140 mg/dl at second visit, not on a stable dose of SU at baseline or dose of metformin>1000mg/day or SU dose too low (glyburide or gliclazide<10 mg/day, glimepiride<4mg/d, gliclazide<160mg/d) |
| Comaschi, 2007[25](#_ENREF_25)  Italy  Not extracted | Neither year reported  6 Months | Run-in period but number excluded was NR | < 6 months | Yes | 398/250  NR | Age <35 yrs, HbA1c < 7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3months, fasting C-peptide <0.33 nmol/L |
| Davies, 2007[26](#_ENREF_26)  United Kingdom  Not extracted | Neither year reported  4 months | Run-in period but number excluded was NR | < 6 months | NR | NR/82  NR | Age <30 or >80 yrs, history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), contraindication or history of intolerance to metformin, HbA1c >7.0%, BMI >43 kg/m2, not using adequate contraception, history of previous insulin use for >2 wks, duration of Type 2 DM <12 months, c-peptide levels <0.33, severe concurrent disease, serum Cr >150umol/l |
| DeFronzo, 1995[27](#_ENREF_27)  US  Not extracted | Not extracted  29 wks (planned duration) | Not extracted | Not extracted | NR | Not extracted | Age <40 or >70 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other |
| DeFronzo, 2005[28](#_ENREF_28)  US  NR | 2002  2003  30 wks | Yes | Not extracted | Yes | NR/336  NR | Fasting glucose >13.3 mmol/l. Not on metformin >=1500mg/day for at least 3 months before screening. If weight not stable (=/-10%) for 3 months before screening. Female subjects were not postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout the study. Use of sulfonylureas, meglitinides, thiazolidinediones,-glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug, or e. |
| DeFronzo, 2009[29](#_ENREF_29)  NR | Neither year reported  24 wks | Yes | < 6 months | Yes | 1462/743  NR | Age <18 or >77 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, neuropathy, retinopathy, HbA1c < 7% or >10%, BMI >40 kg/m2, pregnant, nursing, alcohol or drug abuse, NYHA III and IV, LVEF <40% |
| DeFronzo, 2010[30](#_ENREF_30)  US  Not extracted | Start Year 2006  End Year 2008  20 wks | No run-in period | < 6 months | Yes | NR/137  NR | Age <18 or >75 yrs, HbA1c <6.8% or >10%, BMI <25 kg/m2 or >40 kg/m2, not on stable dose of metformin for at least 6 wks, body weight stable for past 6 months, islet cell auto-antibodies, treatment with any other ODM (other than metformin) |
| DeFronzo, 2012[31](#_ENREF_31)    Multi-continent    NCT00855166 | Neither year reported  26  Wks | Yes | Not Extracted | Yes | NR/  1554    NR | Age <18 or >80 yrs, HbA1c > 10% before and after run-in/stabilization period or <7.5% before and after run-in/stabilization period, BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopathy, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men, <10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization |
| Del Prato, 2015[32](#_ENREF_32)  Multi-continent  NCT00660907 | Neither year reported  208 wks | No | Not extracted | Yes | NR/814  NR | Reference to other studies. |
| Del Prato, 2014[33](#_ENREF_33)  Mutli-continent  NCT00856284 | Neither year reported  104 wks | Yes | Not extracted | Yes | NR/2639  NR | Systolic blood pressure >150mm hg. Diastolic blood pressure >90 mm hg. History of cancer. Prior use of any other diabetes drug for the last 2 months. |
| Derosa, 2004[34](#_ENREF_34)  Italy  Not extracted | Not extracted  12 months (planned duration) | Not extracted | Not extracted | NR | Not extracted | Age <46 or >67 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other |
| Derosa, 2005[35](#_ENREF_35)  Italy  Not extracted | Neither year reported  12 Months | No run-in period | < 6 months | NR | NR/99  case-report forms or computerized clinic registers | Age ≤18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c <7.5%, BMI ≤25.3 kg/m2, pregnant, nursing, not using adequate contraception, if no Type 2 DM for minimum 6 months based on ADA criteria, if no metabolic syndrome based on NCEP ATP III, if no hypertension, triglycerides ≤150mg/dl, C-peptide ≤1.0ng/ml, history of ketoacidosis, anemia, receiving lipid-lowering meds, anticoagulation, glimepiride, or a TZD |
| Derosa, 2005[36](#_ENREF_36)  Italy  Not extracted | Neither year reported  12 Months | No run-in period | < 6 months | NR | NR/99  case notes and/or clinic registers | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), neuropathy, retinopathy, HbA1c < 7%, pregnant, nursing, not using adequate contraception, no type 2 DM by ADA criteria for at least 6 mo, fasting c-peptide <1.0ng/ml, no metabolic syndrome with at least 3 components (based on NCEP ATP III), ketoacidosis, anemia, cerebrovascular conditions within 6 months, consumption of glimepiride or TZDs or prior intolerance to these medications |
| Derosa, 2005[37](#_ENREF_37)  Italy  Not extracted | Not extracted  12 months (planned duration) | Not extracted | Not extracted | NR | Not extracted | Age <18 yrs, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <7.5%, no Type 2 DM, other |
| Derosa, 2009[38](#_ENREF_38)  Italy  Not extracted | Neither year reported  15 Months | Fewer than 10% of participants were excluded during run-in | < 6 months | NR | 271/252  Outpatient primary care, computerized clinic registry | Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5%, BMI <25 kg/m2 or >30 kg/m2, pregnant, nursing, not using adequate contraception, no Type 2 DM, history of ketoacidosis, severe anemia |
| Derosa, 2010[39](#_ENREF_39)  Italy  Not extracted | Neither year reported  12 months | No run-in period | < 6 months | No | 128/128  patients identified from case notes and clinical registers | Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c < 8%, BMI <25 kg/m2 or ≥30 kg/m2, pregnant, nursing, not using adequate contraception, history of ketoacidosis, severe anemia, not intolerant to metformin at maximum dosage (3,000 mg/day), not on metformin, diabetic neuropathy |
| Derosa, 2011[40](#_ENREF_40)    Italy  NCT00660907 | Neither year reported  12  Months | No | Not Extracted | No | NR/  111  Inpatient/hospital  Outpatient: primary care | Age < 18 yrs, HbA1c <=8%, BMI <25 or >=30 kg/m2, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, not taking 1000-2000 mg/d of metformin, history of ketoacidosis, history of cerebrovascular condition, severe anemia, serious CVD (eg, NYHA classes II-IV CHF or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment also were excluded, not intolerant of metformin 2500-3000 mg/d |
| Derosa, 2012[41](#_ENREF_41)    Italy  NCT00601250 | Neither year reported  12  Months | Yes | Not Extracted | No | NR/  178    outpatient clinic within a hospital but not further specified | Age <=18yrs ,HbA1c <=8%, BMI <25 and >= 33kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, severe anemia, Patients with serious cardiovascular disease (CVD) (e.g., NYHA class I-IV CHF or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months |
| Derosa, 2013[42](#_ENREF_42)    Italy  NCT00309608 | 2008  2010    12  Months | Yes | Not Extracted | NR | NR/  178    NR | Age <=18 yrs, HbA1c <=7.5%, BMI <25 or >=31 kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, ketoacidosis, severe anemia, NYHA 1-4 congestive heart failure |
| Derosa, 2013[43](#_ENREF_43)    Italy    NCT00395512 | 2008  2010    12  Months | Yes | Not Extracted | No | NR/  171  NR | Age <=18 yrs, HbA1c <=7.5%, BMI<25 or >=34.9kg/m2, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, history of ketoacidosis, acute or chronic pancreatitis, severe anemia, serous CVD (e.g. NYHA class 1-4 CHF, MI, stroke) or cerebrovascular conditions within 6 months before study enrollment, taking gygtemic glucocorticoids, taking weight reducing drugs such as sibutramine or orlistat, or any medications that miht preclude safe participation in the study |
| Diamant, 2010[44](#_ENREF_44)    Multi-continent  NCT00286442 | 2008  2009    26  Wks | Yes | Not Extracted | Yes | NR/  321    NR | Age 18 yrs or older, HbA1c >11% or <7.1%, BMI <25kg/m2 and >45kg/m2, Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoids, treatment for longer than 2 wks with insulin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening |
| Einhorn, 2000[45](#_ENREF_45)  US  Not extracted | Not extracted  16 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c <8.0%, no Type 2 DM, other |
| Erdem, 2008[46](#_ENREF_46)  Turkey  Not extracted | Neither year reported  12 Wks | No run-in period | < 6 months | No | 53/44  outpatient department of internal medicine clinic | Age <30 or >70 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >35 kg/m2, other chronic disease as detected by history and physical |
| Erem, 2014[47](#_ENREF_47)    Turkey    NCT00263276 | Neither year reported  52  Wks | Yes | Not Extracted | No | NR/  60    NR | Age <30 or >70 yrs, HbA1c < 8% when FPG<126mg/dl, <7% if FBG is 126 -139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria, NYHAC Class 3/4 CHF, history of lactic acidosis, malignancy, thyroid disease, or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection |
| Esposito, 2011[48](#_ENREF_48)    Italy    NCT00749190 | Neither year reported  24  Wks | No | Not Extracted | Yes | NR/  110    investigators' practices | Age <30 and >75 yrs, HbA1c >10% or <7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l) |
| Esteghamati, 2014[49](#_ENREF_49)    Iran  NCT01177813 | 2011  2011    12  Wks | No | Not Extracted | No | NR/  98      Outpatient: subspecialty care setting | not newly diagnosed with diabetes, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, current use of oral antihyperglycemic medication sofr treatment of diabetes or other hyperglycemia-associated conditions(e.g. polycystic ovary syndrome), taking corticosteroids, regularly consuming alcoholic beverages |
| Esteghamati, 2015[50](#_ENREF_50)  Iran  NCT01963663 | 2012  2013  3 months | No | Not extracted | No | NR/84  NR | History of over-thecounter vitamin or anti-oxidant supplements. Significant chronic illnesses of the heart, kidney or lung. |
| Farcasiu, 2011[51](#_ENREF_51)    Multi-continent  NCT01012037 | 2006  2009    16  Wks | Yes | Not Extracted | Yes | NR/  302    NR | Age <30 - >75 yrs, HbA1c > 1.8 X ULN or <1.2 X ULN, BMI >40 kg/m2, Any liver disease, metformin <1500mg, on other oral dm med besides metofrmin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle |
| Feinglos, 2005[52](#_ENREF_52)  US  Not extracted | Not extracted  16 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <30 or >81 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <7.0% or >8.5%, no Type 2 DM, other |
| Ferrannini, 2013[53](#_ENREF_53)    Multi-continent  NCT01167881 | Neither year reported  90  Wks | Yes | Not Extracted | Yes | NR/  659    NR | Age <18 or>79 yrs, HbA1c >=10% or <7%, BMI>40, successfully completed one of the two 12-wk dose-finding studies (refid 584 or 1334) |
| Fidan, 2011[54](#_ENREF_54)    Turkey (assumed based on affilations)  NCT01340664 | Neither year reported  12  Wks | Yes | Not Extracted | NR | NR/  40    NR | Age <40 yrs, HbA1c >10% or <7%, Prior use of any diabetes treatment, Any kidney disease, Pregnant, Not using adequate contraception, malignancy, chronic inflammatory diseases, active infection, COPD, lacking combination of the following (HbA1c 8-<10 or FPG <=140) or (HbA1c 7-8 AND (FPG 120-140 or HOMA-IR >3)), class 3-4 coronary insufficiency, not completing uptitration run-in |
| Fonseca, 2000[55](#_ENREF_55)  US  Not extracted | Not extracted  26 wks (planned duration) | Not extracted | Not extracted | NR | Not extracted | Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other |
| Fonseca, 2012[56](#_ENREF_56)    US and Latin America  NCT01159600 | 2009  2010    18  Wks | Yes | Not Extracted | Yes | NR/  282    NR | Adults, HbA1c >11% or <7.5%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradindicated to or history of treatment with saxagliptin |
| Forst, 2010[57](#_ENREF_57)    Europe  NCT00881530 | Neither year reported  12  Wks | Yes | Not Extracted | Yes | NR/  333    NR | Age <21 or >75 yrs, HbA1c >9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase or <7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, <3 months, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening, one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months |
| Forst, 2012[58](#_ENREF_58)    NR  NCT01593371 | Neither year reported  12  Wks | No | Not Extracted | Yes | NR/  44    NR | Age <30- > 65 yrs, HbA1c < =7%, Retinopathy, not on metformin, receiving any other anti-diabetic drugs, SBP >160 mmHg, DBP >90 mmHg, GFR <60, Smoking in last 6 months |
| Forst, 2014[59](#_ENREF_59)    Germany  No | Neither year reported  12  Wks | No | Not Extracted | Yes | NR/  40    outpatient but unclear if primary or specialty care | Age <45 or >75yrs, HbA1c >8.5% or <6.5%, Any liver disease, Any kidney disease, more than one unexplained episode of severe hypoglycaemia within 6 months, pre-treatment with anti-diabetic drugs other than metformin within the last 3 months, uncontrolled hypertension (SBP>160mmHg, and/or DBP>90mmHg), MI or stroke in last 6 month |
| Gallwitz, 2011[60](#_ENREF_60)    Germany  NCT00885378 | Neither year reported  26  Wks | No | Not Extracted | Yes | NR/  363    NR | Adults, HbA1c >10% or <6.5%, not on metformin |
| Gallwitz, 2012[61](#_ENREF_61)    Multi-continent  NCT00562172 | 2008  2010    104  Wks | Yes | Not Extracted | Yes | NR/  1552    Outpatient: primary care  Outpatient: subspecialty care setting | Age <18, >80 yrs, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening |
| Gallwitz, 2012[62](#_ENREF_62)    Multi-continent  No | 2006  2011    48  Months | No | Not Extracted | Yes | NR/  1029    NR | Age <18 or >85 yrs, HbA1c >9% or <6.5%, BMI <25 or >=40 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides |
| Garber, 2002[63](#_ENREF_63)  US  Not extracted | Not extracted  20 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, treatment experienced, HbA1c <7% or >11%, no Type 2 DM, other |
| Garber, 2003[64](#_ENREF_64)  US  Not extracted | Not extracted  16 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <20 or >79 yrs, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other |
| Garber, 2006[65](#_ENREF_65)  US  Not extracted | Not extracted  24 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <20 or >78 yrs, any liver disease, any kidney disease, history of CVD, HbA1c ≤7% or ≥12% no Type 2 DM, other |
| Garber, 2009[66](#_ENREF_66)  US, Mexico  Not extracted | Start year 2006  End year 2007  52 wks | Fewer than 10 % participants excluded during run-in period | < 6 months | Yes | NR/746  NR | Age <18 or >80 yrs, HbA1c <7% or >11% if prior treatment was diet; >10% if prior treatment was drug, BMI >45 kg/m2, either not treated with diet and exercise or up to half the highest dose of oral antidiabetic drug monotherapy for at least 2 months prior to trial, insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations 5 times upper normal range) |
| Garber, 2011[67](#_ENREF_67)  US    Mexico  No | 2006  2008    104  Wks | No | Not Extracted | Yes | NR/  746    NR | Age <18 or >80 yrs, HbA1c >11% if on diet/exercise or >10% if on monotherapy or <7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia |
| Genovese, 2013[68](#_ENREF_68)    Italy  NCT00511108 | Neither year reported  24  Wks | Yes | Not Extracted | Yes | NR/  213  NR | Age <35 or >75 yrs, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin, acute or chronic pancreatitis or familial polyposis, history of chronic alcohol or drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria |
| Genovese, 2013[69](#_ENREF_69)    Country NR  No | Neither year reported  16  Wks | Yes | Not Extracted | Yes | NR/  58    Outpatient: subspecialty care setting | Age <35 or >75 yrs, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures, participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, CHF (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids,, known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients ( pioglitazone, met marked above) |
| Goke, 2010[70](#_ENREF_70)    Multi-continent  No | 2007  2010    104  Wks | Yes | Not Extracted | Yes | NR/  858    NR | Age <18 yrs, HbA1c >10% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Γüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment, congestive heart failure, significant cardiovascular history within the past 6 months |
| Goldstein, 2003[71](#_ENREF_71)  US  Not extracted | Not extracted  18 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% and >12.0%, other |
| Goldstein, 2007[72](#_ENREF_72)  Multi-continent  Not extracted | Neither year reported  24 Wks | Run-in period but number excluded was NR | NR | Yes | 3544/1091  NR | Age <18 or >78 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient with less than 75% compliance during placebo run in period, patient with HbA1c <7.5% or >11 % after diet/exercise run in/wash-out period, patients with fasting glucose >280 mg/dl after run-in period, no Type 2 DM, Type 1 DM |
| Gomez-Perez, 2002[73](#_ENREF_73)  Mexico  Not extracted | Not extracted  26 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other |
| Gupta, 2009[74](#_ENREF_74)  NR  Not extracted | Neither year reported  16 Wks | No run-in period | < 6 months | Yes | 247/51  NR | Age <35 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), pregnant, not using adequate contraception, FPG >200 mg/dL, individuals using orlistat, sibutramine, ephedrine, steroids, significant lung diseases, significant neurologic diseases, baseline BP>140/90 mmHg, prior use of TZD, beta blockers, smokers, alcohol abuse and using drugs, patients using metal objects precluding required scans |
| Gupta, 2010[75](#_ENREF_75)    India  NCT00772174 | Neither year reported  12  Wks | No | Not Extracted | NR | NR/  94    Outpatient: subspecialty care setting | Age <30 yrs , Any kidney disease, History of CVD, Pregnant, Nursing, history of serious or hypersensitivity reactions to any of study drugs, uncontrolled hyper tension, HF NYHA class IV, recent unstable angina, MI, coronary artery bypass surgery, angioplasty within previous 2 months, TIA, cerebrovascular accident, oral contraceptive use, chronic alcohilism |
| Gupta, 2013[76](#_ENREF_76)    India  NCT00363948 | 2012  2013    24  Wks | No | Not Extracted | NR | NR/  167    Outpatient: primary care | Any liver disease, Any kidney disease, Pregnant, Nursing, history of hypersensitivity to sulphonylurea and DPP-IV inhibitors, psychiatric, GI, hematological, metabolic, neurological, hepatic, or renal disorders, clinically significant heart disease (NYHA III or IV), acute infection |
| Haak, 2012[77](#_ENREF_77)    Multi-continent  ACTRN12608000534381 | 2008  2010    24  Wks | Yes | Not Extracted | Yes | NR/  791    NR | Age <18 or >80 yrs, HbA1c >10.5% if on OAD or >=11% if treatment naïve or <7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months |
| Haak, 2013[78](#_ENREF_78)    Multi-continent  IRCT201102275917N1 | 2009  2011    52  Wks | Yes | Not Extracted | Yes | NR/  567    NR | Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication, alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation |
| Hallsten, 2002[79](#_ENREF_79)  Finland  Not extracted | Not extracted  26 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other |
| Hamann, 2008[80](#_ENREF_80)  Multinational Europe, Mexico  Not extracted | Neither year reported  52 Wks | Yes | < 6 months | NR | 818/596  NR | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m2, used any oral antidiabetic drug other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin <11.0 g/dl for men and <10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170mmHg, DBP >100mmHg |
| Hanefeld, 2004  [81](#_ENREF_81)  Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands  Not extracted | Not extracted  NR | Not extracted | Not extracted | Yes | Not extracted | Age <35 or >75 yrs, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other |
| Hanefeld, 2007[82](#_ENREF_82)  Multinational Europe  Not extracted | Neither year reported  52 Wks | Run-in period but number excluded was NR | < 6 months | Yes | NR/598  NR | Age <40 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m2 or >38 kg/m2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG < 7mmol/l or >15 mmol/l, C peptide <0.27 nmol/l |
| Haring, 2014[83](#_ENREF_83)    Multi-continent  NCT00509262 | 2010  2012    24  Wks | Yes | Not Extracted | Yes | NR/  638    NR | Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d, eGFR<30 |
| Henry, 2012[84](#_ENREF_84)    Multi-continent  NCT00754988 | 2008  2009    24  Wks | Yes | Not Extracted | Yes | NR/  603  Inpatient/hospital  Outpatient: primary care  Outpatient: subspecialty care setting | Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), NYHA Class III or IV congestive heart failure, SBP ΓÇí 180 or DBP ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease |
| Henry, 2012[84](#_ENREF_84)    Multi-continent  No | 2009  2010    24  Wks | Yes | Not Extracted | Yes | NR/  641  Inpatient/hospital  Outpatient: primary care  Outpatient: subspecialty care setting | Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), NYHA Class III or IV congestive heart failure, SBP ΓÇí 180 or DBP ΓÇí 110 mmHg., a cardiovascular event within 6 months |
| Hermann, 1991[85](#_ENREF_85)  Sweden  Not extracted | Not extracted  6 months (planned duration) | Not extracted | Not extracted | NR | Not extracted | No Type 2 DM, other |
| Hermann, 1991[85](#_ENREF_85)  Sweden  Not extracted | Not extracted  6 months (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other |
| Hermann, 1994[86](#_ENREF_86)  Sweden  Not extracted | Not extracted  6 months (planned duration) | Not extracted | Not extracted | Yes | Not extracted | No Type 2 DM, other |
| Hermans, 2012[87](#_ENREF_87)    Europe  NCT01006590) | Neither year reported  24  Wks | Yes | Not Extracted | Yes | NR/  286    NR | Age <18 yrs, HbA1c >10% or <7%, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu- cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d |
| Home, 2007[88](#_ENREF_88)  Multinational Europe, Australia and New Zealand  Not extracted | Start year 2000 End year 2002  18 Months | Run-in period but number excluded was NR | >= 6 months | NR | 7428/4458  NR | Age <40 or >75 yrs, HbA1c <7% or >9%, BMI <25 kg/m2 |
| Home, 2009[89](#_ENREF_89)  Multinational Europe  Not extracted | Start year 2001 End year 2003  7.5 Years | Run-in period but number excluded was NR | >= 6 months | Yes | 7428/4458  Outpatient primary care | Age <40 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, BMI <25 kg/m2, pregnant, nursing, not using adequate contraception |
| Iliadis, 2007[90](#_ENREF_90)  Greece  Not extracted | Neither year reported  18 Wks | Run-in period but number excluded was NR | NR | NR | NR/48  Outpatient subspecialty care setting | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), diagnosis of Type 2 DM >3 yrs, use of any diabetes medication, no Type 2 DM, any heart failure |
| Jadzinsky, 2009[91](#_ENREF_91)  Multi-continent  Not extracted | Start year 2006 End year 2008  24 wks | Fewer than 10% participants excluded during run-in period | < 6 months | Yes | 2936/1394  Outpatient Primary care setting | Age <18 or >77 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c <8% or >12%, BMI >40 kg/m2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CV events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test |
| Jain, 2006[92](#_ENREF_92)  US, Puerto Rico  Not extracted | Neither year reported  56 Wks | Run-in period but number excluded was NR | < 6 months | NR | NR/502  NR | Age <18 or >80 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <7.5% or >11.5%, pregnant, nursing, duration of diabetes > than 2 yrs, intolerance to rosiglitazone, pioglitazone, or troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg /day, oral anti-diabetic drugs, concurrent participation in another investigational study, serum creatinine level >1.5 mg/dl for men, 1.4 mg/dl for women, 1+ proteinuria, anemia (<10 g/dl women, <12 g/dl men), BMI ≤20 kg/m2 or >45 kg/m2; hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 yrs |
| Ji, 2015[93](#_ENREF_93)  Multi-continent  NCT01438814 | Start year 2011 End year 2013  14 wks | Run-in period but number excluded was NR | NR | Yes | NR/689  NR | Age <18 or >80, HbA1c>10, HbA1c 7, BMI or weight >45, prior use of any diabetes treatment, prior or current use of insulin, prior or current use of study drug, any liver disease, any kidney disease, contraindication or history of intolerance to metformin, pregnant, nursing, bariatric surgery, cancer, blood dyscrasias, pancreatitis, treatment with anti-obesity drugs within 3 months before consent or any other treatment at the time of screening leading to unstable body weight, glucose >240 mg/dl, acute coronary syndrome, stroke, or transient ischemic attack within 3 months before consent, treatment with systemic steroids, change in dosage of thyroid hormones within 6 weeks |
| Jonker, 2009[94](#_ENREF_94)  Netherlands  Not extracted | Neither year reported  24 wks | Run-in period but number excluded was NR | < 6 months | Yes | 173/78  Outpatient Primary care setting | Age <45 or >65 yrs, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, HbA1c <6.5% or >8.5%, BMI <25 kg/m2 or >32 kg/m2, no Type 2 DM, prior use of TZD/insulin, BP >150/85 mm Hg |
| Kadoglou, 2011[95](#_ENREF_95)    Greece  No | 2006  2008    6  Months | No | Not Extracted | No | NR/  140    NR | Age <50 and >75 yrs, HbA1c <=7%, BMI <=25kg/m2, Any liver disease, Any kidney disease, usage of antidiabetic medications, autoimmune or life threatening illnesses, on diet therapy for diabets for at least 3 mo, CHF (NYHA class IIIV), clinical evidence of cardiovascular (coronary, peripheral arteries), autoimmune or life-threatening diseases, alcohol / drug abuse, uncontrolled hypertension (blood pressure > 170 / 100 mmHg), recently diagnosed / or untreated hormonic disorders, free from microvascular compl, maintained body weight for 3 mo before study |
| Kadowaki, 2013[96](#_ENREF_96)    Japan  No | 2006  2008    12  Wks | Yes | Not Extracted | Yes | NR/  149    NR | Age <20 or >=75yrs, HbA1c >9.4% for patients receiving an OHA other than metformin at screening, >10.5% for patients with metformin only at screening, >10.5% for all patients completing the run-in period, or <6.4% for patients receiving an OHA other than metformin at screening, 6.9% for patients with metformin only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks |
| Kahn, 2006[97](#_ENREF_97)  Multi-continent  Not extracted | Start year 2000 End year 2006  6 Years | No run-in period | NR | Yes | 6676/4360  NR | Age <30 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or >180 mg/dL, history of lactic acidosis |
| Kaku, 2009[98](#_ENREF_98)  Japan  Not extracted | Start year 2005  40 Wks | Yes | < 6 months | Yes | NR/236  NR | Age ≤ 20 and ≥65 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., failed initial treatment), HbA1c <6.5% or >10%, other pre-existing conditions that potentially require hospitalization such as cancer, severe lung, GI, pancreatic and hematological disorders, history of lactic acidosis, ketoacidosis, diabetic coma, or pre-coma within the preceding 26 wks, if on any medications that might affect glycemic control, drug or alcohol dependency |
| Kaku, 2011[99](#_ENREF_99)    Japan  No | 2006      52  Wks | Yes | Not Extracted | Yes | NR/  411    NR | Age <20 yrs, HbA1c >10.4% or <7.4%, not able to self monitor blood glucoses |
| Kato, 2009[100](#_ENREF_100)  Multinational Europe  Not extracted | Neither year reported  12 wks | No run-in period | NR | NR | NR/50  NR | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, retinopathy, no Type 2 DM, no metabolic syndrome, not on continuous diet/exercise therapy, no anemia, no history of heart failure |
| Kikuchi, 2012[101](#_ENREF_101)    Japan  NCT00359762, EudraCT 2005-005448-21 | 2005  2007    28  Wks | No | Not Extracted | Yes | NR/  373    NR | Age <20 - >75 yrs, HbA1c <7.4%, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60, hemoglobinopathy, edema, unstable or serious angina, MI in past year, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy, serious neuropathy requiring tx |
| Kim, 2007[102](#_ENREF_102)  South Korea  Not extracted | Neither year reported  12 Wks | Fewer than 10% of participants were excluded during run-in | < 6 months | No | NR/120  Outpatient primary care, Outpatient subspecialty care setting | Age <30 or >70 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), duration of diabetes >5 yrs, not on a stable medication with a SU and/or alpha glucosidase inhibitor for at least 3 months, episodes of ketonuria or ketoacidosis, current malignancy, tuberculosis, rheumatic disease, thyroid disease, corticosteroid treatment, previous TZD or metformin treatment |
| Kim, 2014[103](#_ENREF_103)    South Korea  NCT00751114 | 2007  2009    26  Wks | Yes | Not Extracted | Yes | NR/  209    NR | HbA1c >10% or <7%, , Pregnant, treated with metformin 500-1000mg alone for at least 4 wks prior to study, unable to complete diary to monitor SMBG, acute complications such as diabetic ketoacidosis, hyperglycemic hypoerosmolar state within 3 months, clinically significatn renal or hepatic disorders |
| Kiyici, 2009[104](#_ENREF_104)  Turkey  Not extracted | Neither year reported  52 wks | No run-in period | < 6 months | No | NR/50  Outpatient subspecialty care setting | Age <30 or >65 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >8%, BMI >40 kg/m2, GI disease, rheumatological, or neoplastic, infectious diseases, history of using anti-diabetic medications, any endocrine disease except diabetes or hyperlipidemia, smoking, microvascular complications of diabetes, history of substance abuse |
| Kvapil, 2006[105](#_ENREF_105)  Multinational Europe  Not extracted | Neither year reported  16 Wks | No run-in period | < 6 months | NR | NR/341  NR | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria is not adequately controlled on metformin |
| Lavalle-Gonzalez, 2013[106](#_ENREF_106)    Multi-continent    NCT00813995 | Neither year reported  56  Wks | Yes | Not Extracted | Yes | NR/  1284    NR | Age <18 or >80 yrs, HbA1c >10.5% or <7%, Prior or current use of insulin, Any kidney disease, not on MFM (ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG) ΓëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome proliferator-activated receptor ╬│ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening;, CVD(including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening, uncontrolled HTN |
| Lawrence, 2004[107](#_ENREF_107)  UK  Not extracted | Not extracted  12 titration and 12 maintenance wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <45 or >80 yrs, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes <7% or >10% and for low-dose ODM >7.5%, no Type 2 DM, other |
| Leiter, 2005[108](#_ENREF_108)  Canada  Not extracted | Neither year reported  32 Wks | No run-in period | < 6 months | Yes | 720/613  Outpatient primary care | Age <20 or >80 yrs, HbA1c <9.5%, no Type 2 DM, FBG <7 and >14 mmol/l |
| List, 2009[109](#_ENREF_109)  US  Canada, Mexico, Puerto Rico  NCT00297063 | 2005  2006    12  Wks | Yes | Not Extracted | Yes | NR/  389    "98 clinical centers" | Age <18 or >79 yrs, HbA1c >10% or <7%, BMI >40 kg/m2, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml |
| Madsbad, 2004[110](#_ENREF_110)  Multinational Europe  Not extracted | Start year 2000 End year 2001  12 wks | No run-in period | < 6 months | Yes | 311/193  Outpatient Primary Care setting | Age <30 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), HbA1c < 7.5% or >10% on diet treatment, BMI >40 kg/m2, pregnant, nursing, not using adequate contraception, no Type 2 DM, no treatment for DM with ODM or diet, HbA1c >9.5% on ODM, history of CHF, NYHA class III, IV, use of TZDs or other investigational drugs |
| Maffioli, 2013[111](#_ENREF_111)    Italy  NCT 01208012 | Neither year reported  6  Months | Yes | Not Extracted | No | NR/  170    outpatient care - unclear if specialty or primary care | Age <18 yrs, HbA1c <8.0%, BMI < 25.0 or >34.9 kg/m2, Prior use of any diabetes treatment, Any kidney disease, History of CVD, Neuropathy, Retinopathy, Pregnant, Nursing, Not using adequate contraception, does not have hepatic steatosis by ultrasound diagnosis, history of ketoacidosis, muscle toxicity, serum creatine phosphokinase values higher than 2 times the ULN, severe anemia, known contraindications to pioglitazone, glibenclamide, or HMG-CoA inhibitors |
| Malone, 2003[112](#_ENREF_112)  14 countries not specified  Not extracted | Neither year reported  16 Wks | Fewer than 10% of participants were excluded during run-in | < 6 months | Yes | NR/597  subgroup completing test | Age <30 or >75 yrs, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days |
| Marre, 2002[113](#_ENREF_113)  Netherlands, Denmark, Portugal, France, Belgium  Not extracted | Not extracted  4 months (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <18 yrs, any liver disease, any kidney disease, history of CVD, other |
| Moon, 2014[114](#_ENREF_114)    Korea  NCT00676338 | 2007  2009    48  Wks | Yes | Not Extracted | Yes | NR/  75    NR | Age <18 or >75 yrs, HbA1c >12.00% or <7.50%, BMI>=35kg/m2, Any liver disease, Any kidney disease, not on metformin monotherapy (at a dose of >1000mg/day for 3 months prior to enrollment), Taking medications (other than antidiabetic medications) known to affect glycemic control such as glucocorticoids |
| Nakamura, 2000[115](#_ENREF_115)  Japan  Not extracted | Not extracted  3 months (planned duration) | Not extracted | Not extracted | NR | Not extracted | Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other |
| Nakamura, 2004[116](#_ENREF_116)  Japan  Not extracted | Neither year reported  12 Months | No run-in period | >= 6 months | NR | NR/45  Inpatient/hospital | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >6.5%, BP <140/90 mm Hg, controlled on diet alone, C-peptide <0.33 mmol/l, creatinine <1.5 mg/dL, no antihypertensive medications, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease |
| Natali, 2004[117](#_ENREF_117)  London and Italy  Not extracted | Not extracted  16 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, neuropathy, retinopathy, HbA1c >10% after washout, other |
| Nauck, 2007[118](#_ENREF_118)  US, Multinational Europe, Multi-continent  Not extracted | Neither year reported  52 Wks | Yes | < 6 months | Yes | 2141/1172  NR | Age <18 or >78 yrs, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia |
| Nauck, 2009[119](#_ENREF_119)    Multi-continent  NCT00960076 | Neither year reported  26  Wks | Yes | Not Extracted | Yes | NR/  527    NR | Age <18 or >80 yrs, HbA1c >10.00% or <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months, after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen, h/o cardiac surgery or CVDin last 6 months, history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 yrs), laser treatment for proliferative diabetic retinopathy within 6 months, history of treated diabetic gastroparesis, NYHA Class 3 or 4 heart failure |
| Nauck, 2011[120](#_ENREF_120)    Multi-continent    NCT00393718 | 2008    52  Wks | Yes | Not Extracted | Yes | NR/  814    NR | Age < 18 yrs, HbA1c >10% or <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg, cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment |
| Nauck, 2014[121](#_ENREF_121)    Country NR  No | Neither year reported  52  Wks | Yes | Not Extracted | Yes | NR/  1098        NR | Age <18 or >75 yrs, HbA1c >= 9.5% or <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry |
| Oz Gul, 2010[122](#_ENREF_122)    Turkey  UMIN000004582 | Neither year reported  12  Wks | No | Not Extracted | NR | NR/  60    NR | Prior use of any diabetes treatment, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, Pregnant, Nursing, cerebrovascular conditions, impaired kidney function, statins, ACE inhibitor use, need of insulin for acute complications, any medications known to affect sRAGE metabolism |
| Pavo, 2003[123](#_ENREF_123)  Russia and Hungary  Not extracted | Not extracted  32 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <40 yrs, any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <7.5% or >11.0%, no Type 2 DM, other |
| Perez-Monteverde, 2011[124](#_ENREF_124)    Country NR  NCT00661362 | Neither year reported  12  Wks | Yes | Not Extracted | Yes | NR/  492    NR | Age <18 - >78 yrs, HbA1c >12% or <7.5%, Contraindication or history of intolerance to metformin, type 1 Diabetes, history of ketoacidosis, symptomatic hyperglycemia, hypersens or contraind to study drug, not taking an antihyperglycaemic agent (AHA) within the previous 3 months and not more than 4 wks cumulatively in the previous 3 year, likely to need a drug that is a CYP2C8 inhib or inducer, symptomatic hyperglycaemia or a site fingerstick glucose < 130 mgΓüä dl or > 320 mgΓüä dl at the randomisation visi |
| Perez, 2009[125](#_ENREF_125)  US, multinational Europe  Not extracted | Neither year reported  24 wks | Run-in period but number excluded was NR | < 6 months | Yes | 1436/600  NR | Age <18 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g., "failed initial treatment"), contraindication or history of intolerance to metformin, HbA1c <7.5% or >10%, BMI >45 kg/m2, pregnant, nursing, triglycerides >500 mg/dL, discontinued metformin and TZD therapy due to lack of efficacy |
| Petrica, 2009[126](#_ENREF_126)    Romania  NCT00097500 | Neither year reported  12  Months | No | Not Extracted | No | NR/  44      Outpatient: subspecialty care setting | HbA1c <7%, no poor glycemic control with previous medication, no stable therapy with metformin for at least 6 months, CKD of non-diabetic origin, symptoms or history of cerebrovascular disease (TIA, stroke), micro/macroalbuminuria, thyroid dysfunction, abnormal albuminuria, microangiogrpahic complications |
| Pfutzner, 2005[127](#_ENREF_127)  Germany  Not extracted | Not extracted  26 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <40 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <6.6% or >9.9%, other |
| Pfutzner, 2011[128](#_ENREF_128)    Germany (assumed based on author affiliations)  NCT00541450 | Neither year reported  24  Wks | No | Not Extracted | Yes | NR/  305    NR | Age <18 - >75, HbA1c <6.5%, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV) |
| Pfutzner, 2011[129](#_ENREF_129)    Multi-continent    NCT00386100 | Neither year reported  76  Wks | Yes | Not Extracted | Yes | NR/  1306    Community  outpatient settings (unspecified) | Age <18 or >77 yrs, HbA1c >12.00% or <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV CHF and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests |
| Pratley, 2010[130](#_ENREF_130)  Multi-continent Europe, US, and Canada  Not extracted | Start year 2008 End year 2009  26 months | No run-in period | >= 6months | Yes | 1302/665  “Office-based”- possibly out patient | Age <18 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemic or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin anti-hypoglycemic in past 3 months |
| Pratley, 2014[131](#_ENREF_131)    Multi-continent    No | Neither year reported  26  Wks | Yes | Not Extracted | Yes | 784    NR | Age <18 yrs or >80 yrs, HbA1c >10% or <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Γëñ 12 and Γëñ 10 g/dL for men and women, respectively), elevated blood pressure (ΓëÑ 150 and ΓëÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy |
| Qiu, 2014[132](#_ENREF_132)    Multi-continent    No | Neither year reported  22  Wks | Yes | Not Extracted | Yes | NR/  279    NR | Age <18 or >80 yrs, HbA1c >10.5% or <7%, Any kidney disease, FPG and/or fasting self-monitored blood glucose 15.0 mmol/L during the pretreatment phase, diabetic ketoacidosis, history of CVD(including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks, not completing the placebo run-in period |
| Ramachandran, 2004[133](#_ENREF_133)  India  Not extracted | Not extracted  14 wks (planned duration) | Not extracted | Not extracted | NR | Not extracted | Age <30 or >60 yrs, treatment experienced, HbA1c >11%, no Type 2 DM, other |
| Raskin, 2007[134](#_ENREF_134)  US  Not extracted | Neither year reported  28 Wks | Run-in period but number excluded was NR | < 6 months | NR | N/NR  NR | Age <18 or >75 yrs, HbA1c ≤8.0%, BMI >40 kg/m2 or weight >125 kg (275lbs), pregnant, nursing, not using adequate contraception, if not on metformin ≥1,000mg /day as a single agent or in ODM combination therapy for at least 3 months before the trial, history of insulin use |
| Reasner, 2011[135](#_ENREF_135)  US  NCT00770653 | 2007  2009    44  Wks | Yes | Not Extracted | Yes | NR/  1250    NR | Age <18 or >78 yrs, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes |
| Ridderstrale, 2014[136](#_ENREF_136)    Multi-continent    NCT00770653 | 2010  2011    104  Wks | Yes | Not Extracted | Yes | NR/  1549    NR | Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization, blood glucose concentration greater than 13┬╖3 mmol/L after an overnight fast during the placebo run-in, confi rmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation |
| Rigby, 2009[137](#_ENREF_137)  US,  Multicontinent  Not extracted | Start year 2007 End year 2008  16 months | No run-in period | < 6 months | Yes | 356/169  NR | Age <18 or >80 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% (6.5% if on metformin combination therapy) or >10% (9.5% if on metformin combination therapy), BMI > 40 kg/m2, LDL <50 mg/dL or triglycerides ≥500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2months insulin, not on metformin for ≥3 months (1500-2550 mg/day), Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 yrs, any serious disorder including pulmonary, hepatic, GI, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 yrs), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening |
| Robbins, 2007[138](#_ENREF_138)  US, Multinational Europe, Multi-continent, India, Australia  Not extracted | Neither year reported  24 Wks | Run-in period but number excluded was NR | < 6 months | NR | 433/317  NR | Age <35 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <6.5% or >11%, pregnant, nursing, not using adequate contraception, patients who were receiving continuous SC insulin injections or a total daily insulin of >2.0 U/kg or who had a change in type or dose of lipid-altering medications or TZD use up to 3 months before the study, fasting triglyceride level >4.5 mmol/L, serum creatinine >134 micromol/L (men) or >109 micromol/L (women) |
| Roden, 2013[139](#_ENREF_139)    Multi-continent    No | 2010  2012    24  Wks | Yes | Not Extracted | Yes | NR/  899  Inpatient/hospital  Outpatient: primary care  Outpatient: subspecialty care setting    academic medical ctrs, hospitals, and private practices | Age <18, <20 in Japan, <18 or >65 in India, HbA1c >10% or 9% in Germany, <7%, BMI >45 kg/m2, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13┬╖3 mmol/L after an overnight fast during the placebo run-in phase and confi rmed by a second measurement),, contraindications to sitagliptin according to the local label,, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent,, any uncontrolled endocrine disorder apart from type 2 diabetes., did not meet inclusion criteria after placebo run-in |
| Rosenstock, 2006[140](#_ENREF_140)  Multi-continent  Not extracted | Start year 2003 to 2004  32 Wks | Yes | < 6 months | Yes | 1252/468  multicenter | Age <18 or >70 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD(e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half lives of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis |
| Rosenstock, 2010[141](#_ENREF_141)    Country NR  NCT00482729 | Neither year reported  26  Wks | Yes | Not Extracted | Yes | NR/  655    NR | Age <18 or >80 yrs, HbA1c >11% or <7.50%, BMI <23 or >45 kg/m2, not drug-naive (current antihyperglycemmic medication or >6 days of any such agent within 3 months of screening), successful glycemic control with diet and exercise for >=2 months prior to screening |
| Rosenstock, 2012[142](#_ENREF_142)    Multi-continent  NCT00327015 | Neither year reported  12  Wks | No | Not Extracted | Yes | NR/  451    NR | Age <18, >65 yrs, HbA1c >10.50% or <7%, unstable weight or BMI <25 or >45 kg/m^2 (<24 or >45 kg/m^2 for Asians), Diagnosed with type 2 diabetes for less than 3 months, On metformin monotherapy dose <1500mg/day, On metformin monotherapy for less than 3 months, Serum creatinine >1.5mg/dl for men and >1.4 mg/dl for women |
| Rosenstock, 2013[143](#_ENREF_143)    Multi-continent  NCT00434954 | Neither year reported  52  Wks | Yes | Not Extracted | Yes | NR/  441    NR | Age <65 or >90 yrs, HbA1c >9.0% for patients on diet and exercise therapy alone,>8.0% for patients on oral antidiabetic monotherapy & >9.0% after washout period without medications within 2 wks or < 6.50%, not able or unwilling to self-monitor blood glucose with a home glucose monitor |
| Rosenstock, 2013[144](#_ENREF_144)    Multi-continent    No | Neither year reported  12  Wks | Yes | Not Extracted | Yes | NR/  495    NR | Age <18 or >80 yrs, HbA1c >9% if on metformin and one other OAD or >10 if on metformin monotherapy or <6.5% if on metformin and one other OAD, <7 if on MFM monotherapy, BMI >40 kg/m2, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ΓëÑ1500 mg/day or maximum tolerated dose);, diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity;, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months., h/o of MI, CVA, or TIA in past 6 mo, HbA1c <7 or >10 at start of placebo run-in, history of clinically relevant allergy/hypersensitivity, treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months |
| Rosenstock, 2015[145](#_ENREF_145)  Multi-continent  NCT01606007 | 2012  2014  24 wks | Yes | Not extracted | Yes | NR/534  NR | No type 2 diabetes. On stable metformin therapy (>/=1,500 mg/day) for >=8 weeks before screening. Have Cpeptide concentrations >/=1.0 ng/mL. Uncontrolled hypertension (systolic blood pressure >/=160 mmHg and diastolic blood pressure >/=100 mmHg) at randomization. Fasting plasma glucose (FPG) >/=270 mg/dL during the 4-week lead-in period. Cardiovascular disease within 3 months of screening, congestive heart failure (New York Heart Association functional class IV). Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or serum creatinine >/=1.5 mg/dL in men or >/=1.4 mg/dL in women. Patients who received any antidiabetic medication, other than metformin, for more than 14 days during the 12 weeks before screening. |
| Ross, 2012[146](#_ENREF_146)    Multi-continent  NCTC00294723 | 2009  2010    12  Wks | Yes | Not Extracted | Yes | NR/  491    NR | Age <18 or > 80 yrs, HbA1c >10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in for or HbA1c < 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, total daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study), treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months |
| Russell-Jones, 2012[147](#_ENREF_147)    Multi-continent  NCT00701090 | 2008  2010    36  Wks | No | Not Extracted | Yes | NR/  820    NR | Adults, HbA1c >11% or <7.1%, BMI <23 - >45 kg/m2, Prior use of any diabetes treatment, unstable weight |
| Schernthaner, 2015[148](#_ENREF_148)  Multi-continent  NCT01006603 | 2009  2012  52 wks | Yes | NR | Yes | NR/720  NR | Age <65, HbA1c>9, HbA1c7, any liver disease, any kidney disease, type 1 diabetes, any antihyperglycaemic therapy other than metformin <8 wks before enrollment, glucocorticoids, cytochrome P450 3A4 inducers, history of ketoacidosis or hyperosmolar non-ketonic coma, haemoglobinopathies, cognitive function problems, alcohol or illegal drug abuse |
| Schernthaner, 2004[149](#_ENREF_149)  Europe  Not extracted | Not extracted  12 months (planned duration) | Not extracted | Not extracted | NR | Not extracted | Age <35 or >75 yrs, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM |
| Schondorf, 2011[150](#_ENREF_150)    Germany  No | Neither year reported  24  Wks | No | Not Extracted | Yes | NR/  46    NR | HbA1c >9.00% or <6.50%, Prior or current use of insulin, Any liver disease, Any kidney disease, not treated with metformin monotherapy in a maximal individually tolerated dose of 850 to 2000 mg, no dyslipidemia, significant cardiovascular disorder (NYHA I-IV), previous treatment with other oral antidiabetes drugs in addition to metformin |
| Schumm-Draeger, 2015[151](#_ENREF_151)  Multi-continent | 2010  2011  NR | Yes | Not extracted | Yes | NR/400  NR | Not on stable dose of MET >=1500mg/day for >= 10 weeks. Weight loss (sx of uncontrolled dm). BP>=160/100. Clinically significant haematological or oncological conditions. Symptoms of poorly-controlled diabetes. |
| Scott, 2007[152](#_ENREF_152)  US  Not extracted | Neither year reported  12 Wks | Run-in period but number excluded was NR | < 6 months | Yes | 2186/743  NR | Age <21 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), Type 1 DM, gall bladder disease, elevated CK |
| Scott, 2008[153](#_ENREF_153)  Multi-continent  Not extracted | Neither year reported  18 Wks | Run-in period but number excluded was NR | < 6 months | Yes | 486/273  NR | Age <18 or >75 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c <7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose >270 mg/dL |
| Seck, 2010[154](#_ENREF_154)  NR  Not extracted | Neither year reported  2 years | Run-in period but number excluded was NR | < 6 months | Yes | 2141/1172  NR | Age <17 or >78 yrs |
| Seino, 2010[155](#_ENREF_155)  Japan  Not extracted | Neither year reported  24 wks | Yes | < 6 months | Yes | NR/464  NR | Age <20 yrs, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c <7% or >10%, BMI >35 kg/m2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide) |
| Seino, 2012[156](#_ENREF_156)    Japan  No | 2008  2009    12  Wks | Yes | Not Extracted | Yes | NR/  288    outpatient, but not specified | Age <20 or >=65 yrs, HbA1c >=10.4% after 8 wks of observation or <6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis, h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, GI disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg |
| Shihara, 2011[157](#_ENREF_157)    Japan  NCT00575588 | 2007  2010    6  Months | No | Not Extracted | No | NR/  191    NR | Age <30 - >75 yrs, HbA1c >=10.4% or <6.9%, Prior or current use of study drug, Any liver disease, Any kidney disease, History of CVD, CHF, Any hematological condition, Any pancreas condition, not committed to stable diet & exercise regimen, use of any dim med in past month, capable of reading consent form |
| Srivastava, 2012[158](#_ENREF_158)    India  NCT00641056 | 2008  2009    18  Wks | No | Not Extracted | NR | NR/  50    Outpatient (not specified if PC or subsp) | Age <=18 yrs, HbA1c >=10% or <=7%, Any liver disease, Any kidney disease, History of CVD, not on metformin monotherapy for at least 3 mo, type 1 diabetes, other terminal illness |
| St John Sutton, 2002[159](#_ENREF_159)  US  Not extracted | Not extracted  52 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <40 or >80 yrs, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other |
| Stewart, 2006[160](#_ENREF_160)  Multinational Europe  Not extracted | Start year 2003 to 2004  32 Wks | Yes | < 6 months | Yes | 1397/526  NR | Age < 18 or > 70 yrs, history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or >9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG <6.0 mmol/l or >8 mmol/l, prior history of exposure to TZDs within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension |
| Suzuki, 2014[161](#_ENREF_161)  Japan  Not extracted | 2009  2012  6 months | No | Not extracted | No | NR/534  Outpatient: subspecialty care setting | Type 1 diabetes. Severe complication of diabetes. Severe renal and liver dysfunction. Pregnant or nursing women and those who might be pregnant. Alcoholism. A history of stroke and cardiovascular events. Any patient whom the investigator judged to be inappropriate for this study. |
| Tan, 2004[162](#_ENREF_162)  Denmark, Finland, Norway, and Sweden  Not extracted | Not extracted  52 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Treatment experienced, HbA1c <7.5% or >11% for patients not receiving ODM, <7.5 or >9.5 for patients receiving ODM, no Type 2 DM, other |
| Tan, 2004[163](#_ENREF_163)  Mexico  Not extracted | Not extracted  NR | Not extracted | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >11% in patients who were not receiving ODMs, and <7.5 or >9.5 in patients who were receiving ODM monotherapy, no Type 2 DM, other |
| Taskinen, 2011[164](#_ENREF_164)    Multi-continent    NCT00637273 | Neither year reported  24  Wks | Yes | Not Extracted | Yes | NR/  701    NR | Age <18 or >80 yrs, HbA1c < 10.0% for metformin monotherapy patients, 9.0% for patients treated with an additional medication; by the start of the placebo run-in, 10.0% for all patients or HbA1c < 7.0% for met mono patients, 6.5% for patients treated with an additional medication; by the start of the placebo run-in, 7.0% for all patients, BMI >40 kg/m2, Any liver disease, Any kidney disease, not receiving met at a dose of >=1500mg/day (or max tolerated dose), more than one other oral antidiabetes medication, antidiabetes medications have changed within 10 wks prior to the date of informed consent or the dose of met was not stable for >=12 wks before randomization, treated with rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, changed dosage of thyroid hormone treatment within 6 wks or were being treated with systemic steroids at the date of informed consent, acute or chronic metabolic acidosis, hereditary galactose intolerance, dehydration, have participated in another trial of an investigational drug within the previous 2 months, acute MI, stroke, or TIA within last 6 months or acute or unstable CHF |
| Taslimi, 2013[165](#_ENREF_165)    Iran  NCT00103857 | 2011  2011    3  Months | No | Not Extracted | No | NR/  60    NR | HbA1c <7%, Prior use of any diabetes treatment, Prior or current use of study drug, Any liver disease, Any kidney disease, Pregnant, Diabetes diagnosed before the age of 30, congestive heart failure |
| Teramoto, 2007[166](#_ENREF_166)  Japan  Not extracted | Neither year reported  24 Wks | Yes | NR | No | 126/92  NR | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), any medication affecting glucose metabolism, history of diabetic ketoacidosis, history of diabetic coma or pre-coma, Cushing’s syndrome, history of allergy to thiazolizinediones, tumor therapy, receiving insulin for severe infection |
| Tosi, 2003[167](#_ENREF_167)\*  Italy  Not extracted | Not extracted  6 months (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, treatment experienced, HbA1c <6.3%, no Type 2 DM, other |
| Turkmen Kemal, 2007[168](#_ENREF_168)  Turkey  Not extracted | Start year 2005  6 Months | No run-in period | < 6 months | NR | 46/46  Outpatient subspecialty care setting | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), patient on diuretics, uncontrolled hypertension |
| Turner, 1999[169](#_ENREF_169)  United Kingdom  Not extracted | Start year 1977 End year 1991  9 Years | Fewer than 10% of participants were excluded during run-in | < 6 months | Yes | NR/4075  23 UKPDS centers | Age <25 or >65 yrs, FPG<6 mmol/l x 2, individuals on diet only therapy who maintained their blood sugars <6 mmol/l on followup visits |
| Umpierrez, 2006[170](#_ENREF_170)  US  Not extracted | Neither year reported  28 Wks | Run-in period but number excluded was NR | < 6 months | Yes | 538/210  Outpatient primary care, Outpatient subspecialty care setting | Age <18 or >79 yrs, HbA1c <7.5% and >10%, BMI <24 kg/m2, diagnosis of Type 2 DM <6 months, no taking stable doses of metformin (1-2.5g/day) or extended-release metformin (0.5 -2.0g/day) as their only ODM for at least 2months prior to the study, C-peptide <0.27nmol/L, subjects treated with insulin, TZDs or SU within 3months prior to study enrollment, history of substance abuse, severe hypoglycemia, acute metabolic complications, clinically significant abnormal baseline laboratory values including hematology, blood chemistry or urinalysis |
| Umpierrez, 2014[171](#_ENREF_171)    Multi-continent  No | 2010  2012    52  Wks | Yes | Not Extracted | Yes | NR/    NR | Age <18 yrs, HbA1c >9.50% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months |
| van der Meer, 2009[172](#_ENREF_172)  Netherlands  Not extracted | Neither year reported  24 Wks | Fewer than 10% of participants were excluded during run-in | < 6 months | Yes | 173/80  NR | Age <45 or >65 yrs, female, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of CVD (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >8.5%, BMI <25 kg/m2 or >32 kg/m2, SBP <150 mmHg, DBP <85 mmHg, prior TZD or insulin use |
| Wang, 2015[173](#_ENREF_173)  China-Philipphines-Malaysia | 2010  2012  24 wks | Yes | NR | Yes | NR/306  NR | Age <18 & >80, HbA1c>10, HbA1c7, BMI>45, prior or current use of insulin, prior or current use of study drug, any liver disease, any kidney disease, history of CVD, confirmed hyperglycemia (glucose 240 mg/dL after overnight fast during wash-out or run-in), current treatment with a TZD, insulin, GLP-1 agonist, DPP-4 inhibitor, or antiobesity drug, alcohol or drug abuse, steroids use |
| Weissman, 2005[174](#_ENREF_174)  US  Not extracted | Not extracted  24 wks (planned duration) | Not extracted | Not extracted | Yes | Not extracted | Age <18 or >75 yrs, any liver disease, any kidney disease, history of CVD, HbA1c <6.5% or >8.5% for patients having received prior combination treatment, HbA1c <7% or >10% prior monotherapy or drug naive patients, no Type 2 DM, other |
| White, 2014[175](#_ENREF_175)    Multi-continent  NCT00885378 | 2009  2010    12  Wks | Yes | Not Extracted | Yes | NR/  160    outpatient | Age <18 and >78 yrs, HbA1c >10% or <7%, BMI >45, Pregnant, Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies |
| Williams-Herman, 2009[176](#_ENREF_176)   NR  Not extracted | Neither year reported  54 Wks | Run-in period but number excluded was NR | NR | Yes | 3544/1091  NR | Age <18 or >78 yrs, HbA1c <7.5% or >11% after screening diet/exercise run-in (which included a wash-out period), lack of adequate compliance (>=75% by tablet count) during 2-week single-blind placebo run-in period, no Type 2 DM |
| Williams-Herman, 2010[177](#_ENREF_177)    Multi-continent  No | Neither year reported  104  Wks | Yes | Not Extracted | Yes | NR/  1091    NR | Age <18 or >78 yrs, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/= 75% compliant in taking study medication, had not developed contraindication to study medication |
| Xu, 2015[178](#_ENREF_178)  China  NCT01147627 | 2010  2012  6 months | No | Not Extracted | No | NR/416  NR | Acute or severe chronic diabetic complications or illnesses (ketoacidosis, hyperosmotic state, lactic acidosis, severe microand macro-vascular complications, and hepatic dysfunction). Presence of glutamic acid decarboxylase antibodies. Use of drugs affecting gastrointestinal motility, weight and glycaemia. History of pancreatitis. Triglyceride (TG) levels ΓëÑ5 mmolL-1. Body weight not atble over the last 3 months. |
| Yamanouchi, 2005[179](#_ENREF_179)  Japan  Not extracted | Not extracted  12 months (planned duration) | Not extracted | Not extracted | NR | Not extracted | Any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, retinopathy, HbA1c <7.0%, no Type 2 DM, other |
| Yang, 2011[180](#_ENREF_180)    Multinational Asia (China - India – SouthKorea  No | Neither year reported  24  Wks | Yes | Not Extracted | Yes | NR/  570    NR | Age <18 yrs, HbA1c >10% or <7%, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducersHemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past year, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhibitor |
| Yang, 2011[181](#_ENREF_181)    Asia - Korea, China, India  No | Neither year reported  16  Wks | Yes | Not Extracted | Yes | NR/  929    NR | Age <18 and >80 yrs, HbA1c >11% for subjects on OAD monotherapy and 10% for subjects on OAD combination therapy or <7%, BMI >45kg/m2, not treated with one or more oral antidiabetic drugs (OADs) for at least 3 months, treated with insulin within the last 3 months, after run-in with up-titration of metformin to 2000 mg/day and 3-wk maint at that dose, subj with FG 7-12.8 mmol/l could be randomized |
| Yang, 2012[182](#_ENREF_182)    China  No | 2009  2010    24  Wks | Yes | Not Extracted | Yes | NR/  395    NR | Age <18 - >78 yrs, HbA1c >11% or 7.5%, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing |
| Yoon, 2011[183](#_ENREF_183)    Korea  NCT00097500 | 2007  2008    48  Wks | Yes | Not Extracted | Yes | NR/  349    NR | Age <30 - >65 yrs, HbA1c >9.5% or <6.5%, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant |
| Yuan, 2012[184](#_ENREF_184)    China  No | Neither year reported  26  Wks | No | Not Extracted | NR | NR/  59    NR | Age <=18 yrs, HbA1c >10% or <7%, BMI <=28or >=40kg/m2, >=1months, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD |

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not Reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.